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DIGITALIS THERAPY AND INTOXICATION*

Within the past year, three splendid reviews[1-3] concerning digitalis and its derivatives have appeared. Recently too, the writer and his associates[4] have reviewed the physiological and pharmacological properties of the digitalis glycoside, digitoxin. Therefore, in the present article, no attempt will be made to present an encyclopedic survey of the subject of digitalis dosage. Rather an attempt will be made to describe only the methods of digitalis therapy which the author himself has employed in the practical management of patients with cardiac disease. First, however, it may be of value to list some of the principles upon which such therapy has been founded and supported.

I. SOME BASIC PRINCIPLES CONCERNING DIGITALIS THERAPY

A. It is uniformly agreed that digitalis therapy is indicated in the correction of all body fluid derangements and of most atrial arrhythmias when either or both are initiated by (1) acquired or congenital valvular heart disease, (2) acute or chronic hypertensive heart disease, (3) arteriosclerotic heart disease, and (4) cor pulmonale. No such unanimity of agreement, however, exists about the use of digitalis therapy for the correction of these same disorders or of any others when they are caused by other types of cardiac disease.

B. If one particular kind of cardioactive digitalis preparation is found to be effective in a given case, it is likely that all types of cardioactive preparations also will prove to be effective in the same case. Similarly, if a patient proves unduly sensitive to the toxic effects of one preparation, generally he will prove sensitive to all types of preparations.

C. If a digitalis preparation is to benefit a patient suffering from congestive heart failure, its action must induce in the end, a significant diuresis.

D. There is no average "therapeutic" dose for any digitalis preparation. The best that can be obtained is an average "range" of values extending from the average *minimal* effective dose to the average toxic dose. Thus, similar to insulin, the exact dose of a digitalis preparation within this range must be determined for each patient, except that in digitalis administration, this is done primarily by careful observation of the fluid, rhythm and rate changes that may occur after its administration.

E. The guiding principle, therefore, in the initial digitalization and the later maintenance of digitalization in a patient should be: Administer digitalis preparations until not maximum but practical therapeutic efficiency is reached. Slight ankle edema or an occasional increase in the irregularity of the pulse is much less uncomfortable than vomiting, and infinitely safer than ventricular fibrillation.

F. Any patient previously undigitalized who shows no improvement whatsoever either in his deranged fluid or rhythm mechanisms, 24 hours after he has received a half of the total digitalizing dose to be given, will rarely experience total or even partial relief when the total dose has been given.

G. A patient relieved of congestive heart failure by administration of a digitalis preparation, may not relapse into failure immediately or even much later after the drug has been discontinued and all traces of it have disappeared in the body. This fact should be remembered when cardiac patients are treated with rapidly dissipated drugs.

II. DIGITALIS DOSAGE

A. Choice of Preparation

1. *Oral Preparation.* The choice of digitalis preparation for oral administration has been discussed for so many decades that the casual observer might be inclined to believe that it is a matter of considerable importance. The writer, curious about the combined effects of advertising and various types of medical sponsorships upon the administration of various preparations, attempted to discover the national tendencies in respect to choice of preparation. Finding this impossible, he obtained the monthly dispensing rates of various preparations at (a) the pharmacy of a large private hospital, (b) the pharmacy of a medical school hospital, and (c) the pharmacy of a large medical office building. The results are listed in Table I.

Although this is a sampling valid at best for San Francisco, nevertheless because so many of this city's physicians were trained in medical institutions elsewhere, the findings may have more than regional significance.

Inspection of the table makes it clear that a considerable number of patients, whether treated in the private or medical school hospital or treated at home, still receive the "green powder" Withering employed 170 years ago. The far greater use of injectable preparations at the private hospital is believed due to the fact that the particular hospital studied admits many more patients with acute myocardial infarction, many of whom suffer from acute congestive failure. The wide popularity of digitoxin is obvious although the use of digoxin appears to be gaining.

* From the Harold Brunn Institute for Cardiovascular Research, Mount Zion Hospital, San Francisco, California.

TABLE I

Digitalis Preparation	Private Hospital No. of Units(1)	Private Hospital Per Cent of Total	Medical School Hospital No. of Units	Medical School Hospital Per Cent of Total	Outside Pharmacy No. of Units	Outside Pharmacy Per Cent of Total
Digitalis Folia	1200	13.3	600	11.3	1000	17.1
Digitoxin	5000	55.5	4000	75.6	3350	57.2
Digoxin	1000	11.1	250	4.7	1040	17.6
Misc. Glycoside Mixtures	302	3.3	200	3.8	440	6.8
Injectable Glycosides ...	1500	16.7	240	4.5	36	0.6
Total:	9002		5290		5866	

(1) A unit of any preparation listed has been calculated as the pharmacological equivalent of 0.1 mg. of digitoxin.

The writer prefers digitoxin for oral administration not because of its purity or because of its gravimetric standardization but for the following reasons. First, because unlike any other known glycoside or mixture of glycosides (including the leaf itself) it is not only completely absorbed but it is also regularly absorbed under almost all conditions following both oral and parenteral administration. Secondly, it undergoes a slow, but regular excretion and destruction within the body allowing it to exert a prolonged steady and predictable effect. Thirdly, it is the only digitalis preparation about which such data is known.

But just as in cases of "fragile" diabetes, there is a need for the use of a rapidly acting, quickly dissipated type of insulin, so in the very rare instance, a cardiac patient may be seen in whom the margin between therapeusis and intoxication following the administration of a digitalis product is so slight, that a drug must be given whose disappearance rate is rapid (e.g., digoxin, Digilanid, gitalin). It should be stressed however that this thin margin has not been increased thereby, nor will the rate of incidence of toxicity be diminished (it is sometimes increased) but only the duration of the toxic phase may be shortened. Furthermore, it is usually the aged individual in and out of failure and who frequently needs adjuvant therapy who is most apt to exhibit a "fragile" response to digitalis substances. Such a patient's ability to excrete digitalis substances however is profoundly impaired[5]. Therefore, an implicit belief that the supposedly quickly excreted digitalis preparations will also be similarly excreted in this type of patient is an assumption not only unproven by objective data but frequently contradicted by the clinical responses of the patient.

2. *Parenteral Administration.* It is both unwise and unnecessary in the writer's opinion ever to treat acute or chronic congestive heart failure by parenteral injection of either partial, total, or so-called diagnostic doses unless (a) acute pulmonary edema is present or threatens and (b) there is no other feasible portal of absorption. It is also unwise to treat an atrial arrhythmia by this means unless the latter is distinctly life menacing or other drugs have proved worthless.

Since as defined above, this mode of administration is an emergency measure, the digitalis preparation to be used should be one which is capable of exerting its cardioactive effect in the minimal amount of time. The two most commonly used preparations are the pure glycoside, digoxin, and the mixture of precursor glycosides (Cedilanid D). Any glycoside or mixture of glycosides obtained from Digitalis lanata which is in injectable form appears to possess this speed of action. Certainly digitoxin is a poor choice if rapid action is desired primarily because unlike the other glycosides mentioned, it fixes itself to circulting plasma albumin.

B. Digitalis Dosage in Adults

1. *For Initial Digitalization.*

(a) Oral Administration. The treatment preferred by the writer is that calling for the least *retained* amount of a digitalis preparation (Digitoxin, 1.0 mg.; Digoxin 2.0 mg.; Gitalin, 4.0 mg.; Digitalis Folia, 1.0 gm.) which given over a period of 72 hours, produces a marked amelioration of the symptoms and signs of congestive heart failure or deranged atrial arrhythmia or both. The administration of the glycoside, digitoxin, will be described in detail because, frankly, the writer believes it is this drug whose effect is least disturbed by the possibly deranged absorptive and excretory mechanisms present in the acutely congested patient, thus allowing a minimum chance for *unpredictable* toxicity to occur.

In practice then, the patient is given 0.2 mg. of digitoxin twice a day and it is assumed that in 3 days he will have absorbed 1.2 mg. but also will have excreted and destroyed 0.2 mg. leaving him with 1.0 mg. The three day period of digitalization is used because it allows ample time for the patient with congestive heart failure[6] and the patient over 60[5] to excrete at least a modicum of the digitoxin or other preparation administered. These doses may be minimal for individuals of 120 pounds or over but as already pointed out above, if digitalis therapy is to be effective at all, these *approaches* to a total digitalizing dose will produce marked improvement in 72 hours as indicated by symptomatic improvement, or by slowing and regularization of the rhythm and invariably by diuresis if the patient is in congestive failure. If no improvement occurs during

the 72 hour period, then digitalis therapy is probably not to be relied upon and recourse to other measures should be entertained.

(b) Parenteral Administration. As already mentioned, either Cedilanid D or digoxin is the preparation of choice. If Cedilanid D is chosen, 0.8 mg. is slowly injected (over 5 minutes) intravenously. If digoxin is used, 0.5 mg. should be injected. If a therapeutic effect is observed in an hour, an additional 0.4 mg. of Cedilanid D may be given in the former and an additional 0.5 mg. of digoxin in the latter case. But it should be pointed out that similar to the "half dosage point" in oral digitalization, if the initial injection of a partial digitalizing dose results in no improvement, little help should be expected following the injection of the final increment.

If the patient survives, one is faced the next day with the irritating difficulty of deciding the type of oral dosage schedule to be adopted because at this time, the therapist really never knows how much glycoside remains in the body. Furthermore, the administration of a maintenance dose of a rapidly excreted drug may lead eventually to a total but unrecognized loss of total digitalization for the reason given above. The writer prefers, therefore, to administer after a full period of 24 hours, the very slowly excreted glycoside, digitoxin at a dosage of 0.1 mg. t.i.d. for 5 days. Thus as the rapidly excreted injectable glycoside is being dissipated, a gradual retention of digitoxin is being attained. However, it is just this type of situation which is especially favorable to the onset of intoxication and if any doubt exists as to its possible presence, the digitoxin should be omitted or reduced.

2. *For Maintenance.*

The size of the maintenance dose of any digitalis preparation depends upon (a) the nature of the particular preparation used, (b) the muscle mass of the patient (which is not necessarily indicated by total body weight), (c) the age of the patient, (d) the cardiac status of the patient and (e) the possible individual idiosyncrasies of the patient not only in regard to excretion, utilization and destruction but also sensitivity to the preparation given. These factors, never possible of conversion into exact generalizations referable to arbitrary dosage, make the construction of an arbitrarily arrived at "average" dose an absurdity. Remembrance of this last fact will prove to be of infinitely greater therapeutic importance to the reader than his retention of the minimal dosage ranges given by this or any other writer.

If digitoxin is to be used, then a drug will be employed (a) whose absorption is complete (b) whose *maximal* excretion is rarely more than 50 per cent of the daily dosage given and (c) whose *maximal* destruction within the body is rarely more than 50 micrograms per day[5]. Thus, if a patient is assumed to be digitalized (i.e. retaining 1.0-1.2 mg.), the administration of 0.1 mg. (100 micrograms) of digitoxin will lead to a maximal excretion of half of the dose and the remaining half or 50 micrograms will be utilized or destroyed, resulting in no net retention. However, if 0.2 mg. (200 mcg.) is given daily, although half (100 mcg.) will be excreted, still only the relatively fixed amount of 50 mcg. will be destroyed, leading to the *gradual* retention of increasing amounts of digitoxin. This then is the prime reason why, irrespective of the size of the initial digitalizing dose, **the daily administration of 0.2 mg. of digitoxin sooner or later produces toxicity.** The same type of calculation also explains why a dosage of 0.15 mg. also produces toxicity not infrequently. Moreover, since these excretory and destruction rates are probably maximal, there will be more than an occasional patient who, unable to excrete either 50 percent of a daily dose (particularly the aged patient or one with a minimal muscle mass), may become toxic when given 0.1 mg. of digitoxin a day. On the other hand, the daily administration of 0.05 mg. (50 mcg.) of digitoxin usually only covers the daily destruction rate thus allowing some of the initial digitalizing dose to be lost by excretion. In short, many patients could probably best be maintained upon 0.075 mg. of digitoxin a day. Unfortunately no such preparation is available and it can be given only by administering 0.1 mg. of digitoxin five of the seven days of the week,—a method many clinicians now are forced to employ because of the unavailability of the proper dosage tablet.

In view of the above considerations, any adult over 15 and under 60 years of age, weighing over 120 but less than 180 pounds, may be given 0.1 mg. of digitoxin daily; if the patient is over 60 years of age or if he weighs less than 120 pounds, he may be given 0.075 mg. of digitoxin daily by administering 0.1 mg. five of the seven days of the week. Patients weighing over 180 pounds (with muscle mass making up a goodly portion of the weight) may be given approximately 0.125 mg. of digitoxin per day by administering 0.15 mg. per day for five of the seven days of the week. Except under extraordinary conditions, patients should not be *begun* with an average daily maintenance dose of 0.15 mg. of digitoxin, and certainly they should *never be begun with 0.2 mg.*

If digitalis folia is used, substitute gram for mg. in dosages above. If digoxin or gitalin are to be given, multiply above doses by three to five. However, the employment of the spacing technique described above cannot be used easily with these latter two glycosides because of their rapid dissipation. But if a case of "fragile" chronic failure (as defined above) is encountered, a glycoside other than digitoxin may be tried.

After the above scale of doses has been begun, both the patient and the physician should be alert for the possible signs of toxicity on one hand and loss of digitalization on the other. Since the dosages advocated are the minimal effective ones, the possibility of serious toxicity is very rare.

Loss of digitalization in a previous case of failure is primarily indicated by either overt or

TABLE II

Preparation	*Digitalizing Dose*	*Daily Maintenance Dose*
Digitalis folia:		
Infant	15 mg/lb.	1/10 of total
Adult	10 mg/lb.	Dig. Dose
Digitoxin:		
Infant	0.02-0.03 mg/lb.	1/10 of total
Adult	0.01-0.02 mg/lb.	Dig. Dose
Lanatoside D (injectable)		
Infant	0.01-0.02 mg/lb.	1/10 to 1/4 of
Adult	0.008-0.01 mg/lb.	total Dig. Dose

occult fluid retention. But even when occult, its occurrence may be suspected by increasing respiratory or upper abdominal discomfort. Its presence also may be determined by the following simple procedure.

The patient is instructed to collect and measure his total urine output over a period of 16 hours (usually from 4:00 P.M. to 8:00 A.M.). The next day, the same procedure is repeated after the intravenous injection of 1.5 cc. of a potent mercurial diuretic (e.g., Mercuhydrin). If the volume of the second collection exceeds the first by 80 per cent or more, the patient is assumed to have fluid derangement of cardiac origin. Such a positive test, however, does not indicate unequivocally that additional administration of digitoxin will aid the failing heart because mercurials will cause diuresis in the patient in failure long after he fails to respond to a digitalis preparation. With this exception in mind, the patient should be given an additional daily increment of 0.025 mg. of digitoxin and retested again within 7-10 days. If less or no significant increase in urine flow occurs after mercury administration, the dosage should not be increased but maintained.

C. Digitalis Dosage in Infants and Children

The writer has had no experience in the digitalization of these patients. Table II, however, lists the dosages found to be satisfactory by his hospital colleague, S. J. Robinson, M.D., Chief of Pediatrics, Mount Zion Hospital.

III. DIGITALIS INTOXICATION

Serious digitalis intoxication need never arise if (1) a dependably absorbed and excreted preparation is given; (2) if the patient is given minimal effective doses; (3) if each patient is treated and observed as carefully as if he were a diabetic being given insulin; (4) if the patient himself is thoroughly informed of *all* possible symptoms and signs of intoxication; and (5) if the intravenous injection of even small amounts of glycosides is scrupulously avoided except as an immediate life saving procedure.

Such simple rules, however, appear difficult to follow and it is rather certain that a century hence, this same subject will be discussed. At any rate when intoxication does occur, two simple effective counter-measures are to be done. Discontinue the digitalis preparation and, if the patient is not uremic, administer potassium chloride. The latter should always be given orally (2-3 grams q. 3-4 hours) unless a serious life threatening arrhythmia is present. If the latter does occur, a solution containing 5.0 grams of KCl/liter of 5 per cent dextrose solution can be given intravenously at a rate no faster than 4 cc. per minute until the arrhythmia ceases. It is regrettable that although the striking efficacy of this cation in the abolition of digitalis arrhythmias was clearly shown by Sampson, Alberton and Kondo in 1943[7], it has been only recently that this important discovery has been generally recognized[1-2]. Indeed it seems safe to assume that the administration of adequate potassium acts as a specific antidote not only against the arrhythmias induced by overdigitalization but also against all or most of the other symptoms and signs occuring in this syndrome.

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BIBLIOGRAPHY

1. Lown, B., and Levine, S.: Current Concepts in Digitalis Therapy. N. Eng. J. Med. **250:** 771, 819 and 866, 1954.
2. Kay, C. F.: The Clinical Use of Digitalis Preparations. Circulation, **12:** 116, 291, 1955.
3. Goodman, L. S. and Gilman, A.: **The Pharmacological Basis of Therapeutics.** New York, The MacMillan Company, 1955.
4. Friedman, M., St. George, S., and Bine, R., Jr.: The Behavior and Fate of Digitoxin in the Experimental Animal and Man. Medicine, **33:** 15, 1954.
5. Friedman, M., Bine, R., Jr., Byers, S. O., and Bland, C.: The Renal Excretion of Digitoxin in the Normal Subject After Single and Continuous Administration of the Drug. Circulation, **2:** 749, 1950.
6. Friedman, M., St. George, S., Bine, R., Jr., and Byers, S. O.: The Renal Excretion of Digitoxin in the Acute and Chronic Cardiac Patient. Circulation, **6:** 853, 1952.
7. Sampson, J. J., Alberton, E. C., and Kondo, B.: The Effects on Man of Potassium Administration in Relation to Digitalis Glycosides with Especial Reference to Blood Serum Potassium, the Electrocardiogram and Ectopic Beats. Am. Heart J., **26:** 164, 1943.

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ABSTRACTS OF PAPERS

for

THE 29th ANNUAL SCIENTIFIC SESSIONS,

AMERICAN HEART ASSOCIATION

The 29th Annual Scientific Sessions of the American Heart Association will be held in Cincinnati, Ohio, October 27, 28, 29, 1956 in conjunction with the Association's Annual Meeting. Those interested in presenting papers must submit their abstracts by *May 15.* Abstracts will be accepted only on forms which may be obtained from the Medical Director, American Heart Association, 44 East 23rd Street, New York 10, New York.

Papers intended for presentation should be based on original investigations in or related to the cardiovascular field. The abstracts must be 300 words or less and should contain in summary form the results obtained and the conclusions reached. Abstracts must be submitted in triplicate.

The Scientific Sessions this year will feature an enlarged section for Scientific Exhibits. Requests for space and application forms can also be obtained from the Association's Medical Director. The deadline for these applications is May 15, 1956. All exhibit applications will be acted upon by the Program Committee of the Scientific Council.

INTERNATIONAL CARDIOLOGY MEETINGS

Second European Congress of Cardiology

The Second European Congress of Cardiology will be held in Stockholm, Sweden, September 10-14, 1956, under the presidency of Professor Gustav Nylin. The Secretary-General for the Congress is Dr. Karl Erik Grewin, Sodersjukhuset, Stockholm, Sweden.

Fifth Interamerican Congress of Cardiology

The Fifth Interamerican Congress of Cardiology will be held in Havana, Cuba, November 11-17, 1956. Dr. Ramon Aixala of Havana is President of the Cuban Committee for the Congress, which is sponsored by the Interamerican and Cuban Societies of Cardiology. The Secretary-General is Dr. Rafael Perez Diaz, Al Apartado 2108, Havana, Cuba. Those interested in attending this meeting should note that it has been postponed one week from the dates originally announced.

Third World Congress of Cardiology

The Third World Congress of Cardiology will be held in Brussels, Belgium, in September 1958, under the chairmanship of Professor P. Rijlant. The Secretary-General for the Congress is Dr. Fr. Van Dooran, 80 Rue Merceles, Brussels, Belgium.